(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 396 901 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **21.06.95** (51) Int. Cl.[6]: **C07D 499/00**

(21) Application number: **90106310.7**

(22) Date of filing: **02.04.90**

(54) **Process for producing beta-lactamase inhibitor.**

(30) Priority: **12.05.89 US 350966**

(43) Date of publication of application:
14.11.90 Bulletin 90/46

(45) Publication of the grant of the patent:
21.06.95 Bulletin 95/25

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI NL SE

(56) References cited:
EP-A- 0 097 446
EP-A- 0 138 523

(73) Proprietor: **AMERICAN CYANAMID COMPANY**
One Cyanamid Plaza
Wayne, NJ 07470-8426 (US)

(72) Inventor: **Krishnan, Raghavan**
82 Lonergan Drive
Suffern,
New York 10901 (US)
Inventor: **Gamble, Jesse**
5 Elener Lane
Spring Valley,
New York 10977 (US)
Inventor: **Blum, David**
3 Saddle Horn Drive
Upper Saddle River,
New Jersey 07458 (US)
Inventor: **Curran, William V.**
27 Harding Street
Pearl River,
New York 10965 (US)
Inventor: **Lee, Ving J.**
19 Shuart Road
Monsey,
New York 10952 (US)
Inventor: **Conrow, Ranson B.**
50 Lieutenant Cox Drive
Pearl River,
New York 10965 (US)

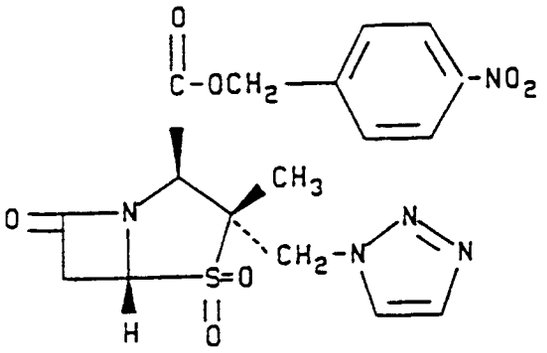
(74) Representative: **Wächtershäuser, Günter, Prof. Dr.**
Patentanwalt,
Tal 29
D-80331 München (DE)

EP 0 396 901 B1

Description

SUMMARY OF THE INVENTION

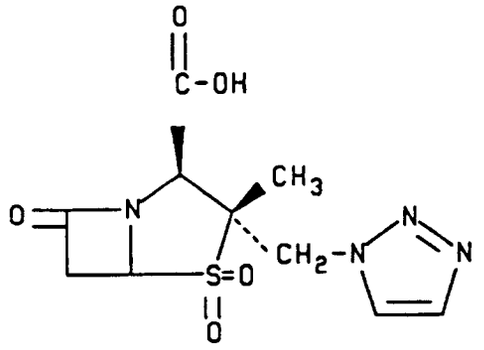
This invention is concerned with an improved process for producing the intermediate [2S-(2α,3β,5α)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 4,4-dioxide, having the structure



The improvement resides in an increased yield (60%) and purity (90%), the elimination of two steps in the heretofor known synthesis and allows isolation directly from the reaction mixture without resorting to chromatography.

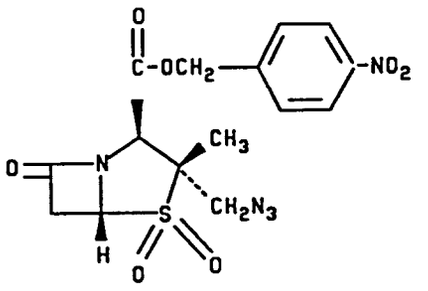
In a known reaction described in EP-A-0097446 strenuous conditions are involved and the product is isolated by column chromatography.

The above described intermediate is then used to produce the biologically active β-lactamase inhibitor [2S-(2α,3β,5α,)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide having the formula

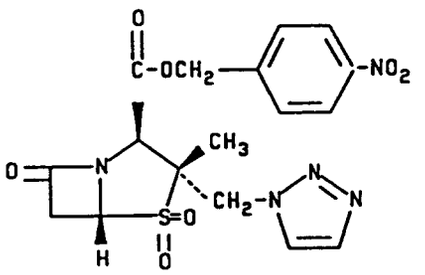


DESCRIPTION OF THE INVENTION

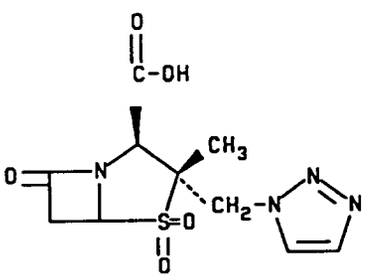
The process improvement which is the subject of this invention is described by the following reaction scheme and description:



1



2



3

According to the above reaction azidopenamsulfone 1 is dissolved in vinyl propionate containing 4-methoxyphenol and this solution is reacted dropwise with a solution of bis(trimethylsilyl)acetamide and 4-methoxyphenol in toluene at 70-80 °C followed by reaction at 95-100 °C for about 24 hours and filtration and cooling to produce the intermediated [2S-(2α,3β,5α,)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 4,4-dioxide, 2 having 90% purity and in 60% yield.

The intermediate 2 is then hydrogenated over 5% palladium on carbon in ethyl acetate/water, containing sodium bicarbonate, followed by acidification with a mineral acid, giving the desired β-lactamase inhibitor 3.

Example 1

[2S-(2α,3β,5α)]-3-Methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, (4-nitrophenyl)-methyl ester 4,4-dioxide

An ethyl acetate solution containing 84 g of azidopenamsulfone was evaporated to dryness, then added to 1865 ml of vinyl propionate containing 4 g of 4-methoxyphenol and stirred for 1 hour. The solution was filtered and the filtrate added dropwise over 3.5 hours to a solution comprised of 1324 ml of toluene, 84 ml (66.8 g) of bis(trimethylsilyl)acetamide and 4 g of 4-methoxyphenol at 70-80 °C. When addition was complete the reaction temperature was raised to 95-100 °C and maintained for 24 hours. The reaction was then cooled to room temperature, combined with 11 g of hydrous magnesium silicate, stirred for 20 minutes and then filtered through a bed of 33 g of hydrous magnesium silicate. The filtrate was rotoevaporated, collecting 2500 ml of distillate. The filtrate was stirred at room temperature for 12 hours, then cooled to 0-5 °C for 2 hours and the resulting solid collected, washed with heptane and dried, giving 50 g of the desired intermediate with a purity of 90%.

Claims

1. A process for producing the compound [2S-(2α,3β,5α)]-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, (4-nitrophenyl)methyl ester, 4,4-dioxide, which comprises reacting a solution of azidopenamsulfone, 4-methoxyphenol and vinylpropionate with a solution of bis(trimethylsilyl)acetamide and 4-methoxyphenol in toluene at 80-100 °C for 18-30 hours followed by filtering the resulting solution and cooling the filtrate to 0-10 °C.

Patentansprüche

1. Verfahren zur Herstellung der Verbindung [2S-(2α,3β,5α)]-3-Methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptan-2-carbonsäure,-(4-Nitrophenyl)methylester,-4,4-Dioxid, das umfaßt die Umsetzung einer Lösung von Azidopentamsulfon, 4-Methoxyphenol und Vinylpropionat mit einer Lösung von Bis(trimethylsilyl)acetamid und 4-Methoxyphenol in Toluol bei 80 bis 100 °C für 18 bis 30 Stunden, gefolgt von Filtration der entstandenen Lösung und Abkühlen des Filtrats auf 0 bis 10 °C.

Revendications

1. Procédé de production du composé 4,4-dioxyde de [2S-(2α,3β,5α)]-3-méthyl-7-oxo-3-(1H-1,2,3-triazol-1-ylméthyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate de (4-nitrophényl)méthyle, qui comprend la réaction d'une solution d'azidopenamsulione, de 4-méthoxyphénol et de propionate de vinyle avec une solution de bis(triméthylsilyl)acétamide et de 4-méthoxyphénol dans le toluène à 80-100 °C pendant 18-30 h puis la filtration de la solution résultante et le refroidissement du filtrat à 0-10 °C.